

Victoza® (liraglutide injection): Major Adverse Cardiovascular Events, Thyroid Cancer, and Calcitonin

**Novo Nordisk
New Drug Application 22-341**

**Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Silver Spring, Maryland
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Center for Drug Evaluation and Research

Outline of Presentation

- **Description of product**
- **Description of development program and exposure**
- **Introduction to review of MACE**
- **Overview of statistical methods considerations (Dr. Derr)**
- **Results of MACE analyses**
- **Data regarding thyroid cancer in humans**
- **Data regarding calcitonin in humans**

Description of Product

- Human glucagon-like peptide 1 analogue
- Proposed indication to improve glycemic control in patients with type 2 diabetes mellitus
- Promotes glucose-dependent secretion of endogenous insulin
- Intended for once daily use
- Initial dose 0.6 mg SQ q day, with weekly titration in 0.6 mg increments to maximum dose of 1.8 mg SQ q day

Development Program

- **38 completed clinical trials at time of NDA submission; 2 more with safety update**
- **5 major Phase 3 trials**
- **Development program not designed prospectively to permit systematic evaluation of cardiovascular events or thyroid cancer**

Liraglutide Exposure at Time of 120-day Safety Update

- **4655 patients had been exposed to liraglutide**
- **Of these, 2412 exposed for ≥ 24 weeks**
- **Of these, 840 exposed for ≥ 50 weeks**
- **About twice as many patients exposed to liraglutide as exposed to comparator**

Overview of Major Phase 3 Trials

- All randomized, controlled, parallel group
- Each had multiple liraglutide dose arms
- No placebo-controlled monotherapy trial in naïve patients
- Trials which used a placebo were add-on
- 4/5 measured primary endpoint at 26 weeks. One measured at 52 weeks.
- Two had voluntary open-label extensions where patients stayed on randomized treatment
- Included total of 2501 liraglutide-exposed patients (59% of total phase 2/3 LGT-exposed pop)

Overview of Major Phase 3 Trials (cont)

- **Study 1573:** monotherapy trial with glimepiride comparator arm
- **Study 1572:** add-on to metformin (comparators add-on placebo or add-on glimepiride)
- **Study 1436:** add-on to glimepiride (comparators add-on placebo or add-on rosiglitazone)
- **Study 1574:** add-on to metformin + glimepiride (comparator add-on placebo)
- **Study 1697:** add-on to metformin + rosiglitazone (comparator add-on placebo or add-on insulin glargine)

Baseline Characteristics of Phase 3 Population

- **54% male**
- **Mean age 56 yrs**
- **Mean DM duration 7.7 yrs**
- **Mean baseline HbA1c 8.4%**
- **Mean BMI 31.3 kg/m²**
- **6.8% diet-only DM treatment**
- **32.6% prior DM monotherapy only**
- **60.6% prior combo DM therapy**

Baseline Characteristics of Phase 3 Population (cont)

- **Trials had exclusion criteria for significant cardiovascular disease and elevated baseline creatinine (generally max 1.3 mg/dL women, 1.5 mg/dL men)**
- **Prior MI: 3.4%**
- **BL hypertension: 66.8%**
- **BL term “hyperlipidemia”: 23.3%**
- **BL term “hypercholesterolemia”: 15.2%**
- **BL term “dyslipidemia”: 16.0%**

Baseline Diabetes Complications (Trials 1572, 1436, 1697)

- **At screening, case report form for concomitant illnesses had section to record these, but no specific definitions used**
- **Nephropathy: 6.1%**
- **Macroangiopathy (includes PVD): 11.4%**
- **Retinopathy: 15.4%**
- **Neuropathy: 19.2%**

Rescue Criteria for Inadequate Glycemic Control in Major Phase 3 Trials

- **Weeks 8-26/28: FPG >239 or >240 mg/dL**
- **During open-label extensions: FPG >220 mg/dL**
- **Rescued patients removed from study, and therefore were not available to experience further adverse events**
- **Rescue withdrawals more common with add-on PBO than with LGT or AC**

Major Adverse Cardiovascular Events (MACE)



Challenges for MACE Review

- Development program had not been designed to be combined into a meta-analysis
- Trials of varying durations, with differences in blinded and open-label extension periods between trials
- Cardiovascular events not prospectively adjudicated and inadequate data to perform post hoc adjudication
- High risk patients had not been specifically included
- Relatively few major adverse cardiovascular events occurred

Endpoints: “Broad MACE”

- Chose a broad endpoint and a more specific endpoint
- For both endpoints, trying to assess occurrence of CV death, myocardial infarction or stroke
- “Broad MACE” included CV death and Standard MedDRA Broad Queries for MI, CNS hemorrhages and cerebrovascular accidents
- MedDRA SMQs are intended as “broad nets”
- Standardized
- Perhaps not very specific for MI or stroke- 46% of events were elevated CPK
- Did not include a few potentially relevant events

Endpoints: “FDA Custom”

- Subset of “Broad MACE”
- More specific; sought to include terms more likely to represent actual events of MI or stroke
- Not a standardized endpoint; efforts made to reduce bias in term selection
- Terms selected by independent review by each of 3 clinical reviewers without consideration of what events had actually occurred. For nonunanimous terms, reached concurrence to include or exclude.
- Others may have chosen different terms for inclusion

Other Elements of Analyses

- **Type of events:** all treatment-emergent events, or only serious events
- **Comparator:** total comparator (pbo + active), with subgroup analyses vs active control alone and vs placebo alone
- **Time period populations:**
 - Population A includes randomized, controlled periods of all Phase 2/3 trials, out to measurement of primary endpoint
 - Population B adds controlled, but unblinded voluntary extensions

Overview of Statistical Methods Considerations



Liraglutide vs. Comparator: Estimation Methods

- **Incidence ratio:**
 - % of patients with events in Liraglutide / % of patients with events in Comparator
 - Upper 95% CI bound compared to noninferiority margins of 1.3 and 1.8
- **Stratified by study:**
 - Best way to provide a meaningful estimate of upper 95% CI bound
 - Estimation is challenging when events are infrequent
- **Results:**
 - Liraglutide/Total Comparator (Placebo + Active) was not sensitive to method
 - Liraglutide/Placebo subgroup was sensitive to method

Liraglutide / Comparator Stratified by Study

Advantage:

- **Provides a meaningful analysis across randomized studies with different allocation ratios**
 - **L:T (all 15 studies) ranged from 5:1 to 0.67:1**
 - **L:P (subgroup of 12 studies) ranged from 6:1 to 2:1**
 - **L:A (subgroup of 9 studies) ranged from 5:1 to 1:1**

Liraglutide / Comparator Stratified by Study

Disadvantage:

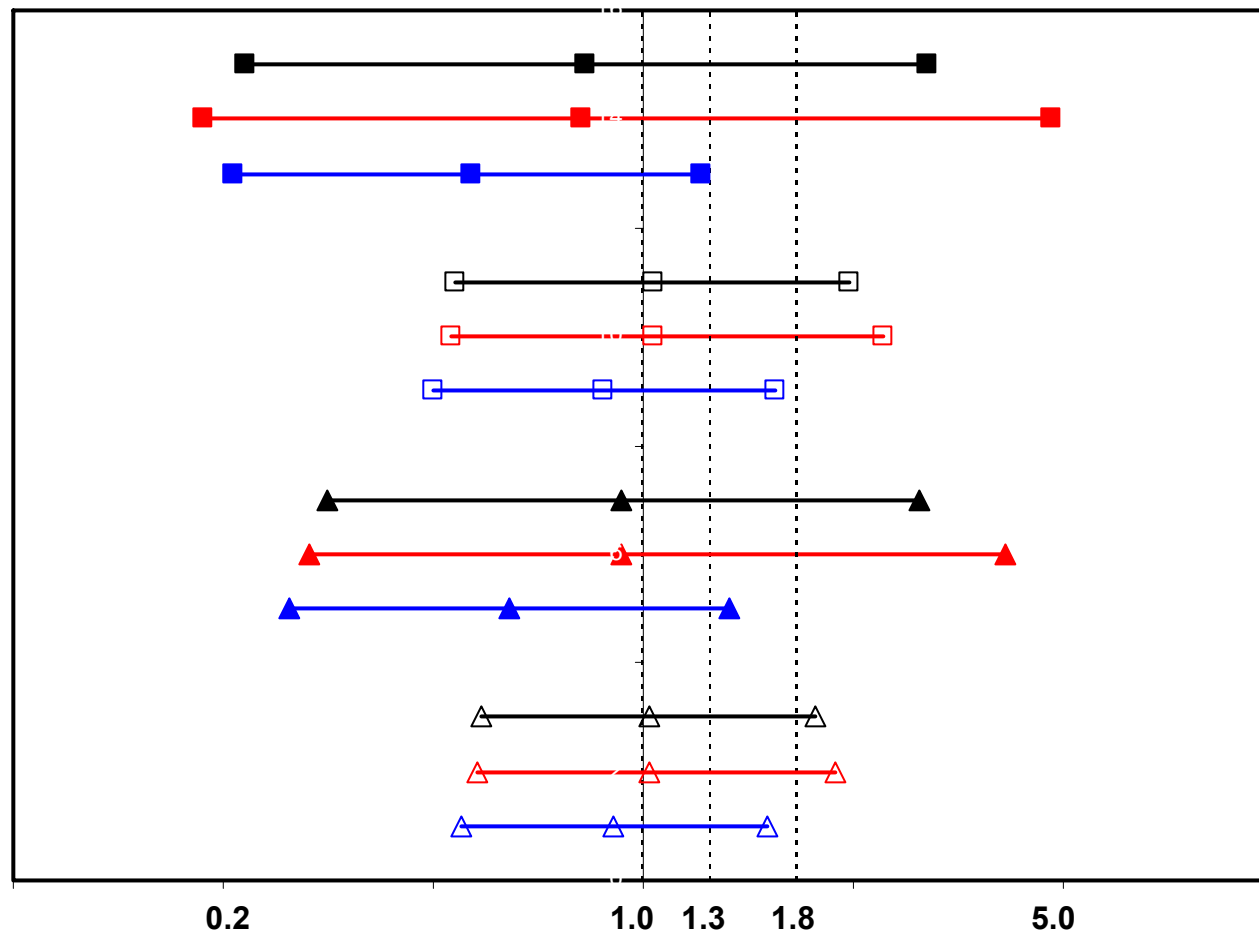
- **When events are infrequent, stratifying by study can create “empty cells” (studies with 0 events in 1 or both groups)**
- **Estimates may be sensitive to method in this situation**

Liraglutide vs. Placebo

(Subgroup of 12 Studies)

Liraglutide vs Placebo, all TEAE, 95% CI

- Custom, CMH, Pop A
- Custom, Exact, Pop A
- Custom, FEMA, Pop A
- SMQ Broad, CMH, Pop A
- SMQ Broad, Exact, Pop A
- SMQ Broad, FEMA, Pop A
- ▲ Custom, CMH, Pop B
- ▲ Custom, Exact, Pop B
- ▲ Custom, FEMA, Pop B
- △ SMQ Broad, CMH, Pop B
- △ SMQ Broad, Exact, Pop B
- △ SMQ Broad, FEMA, Pop B



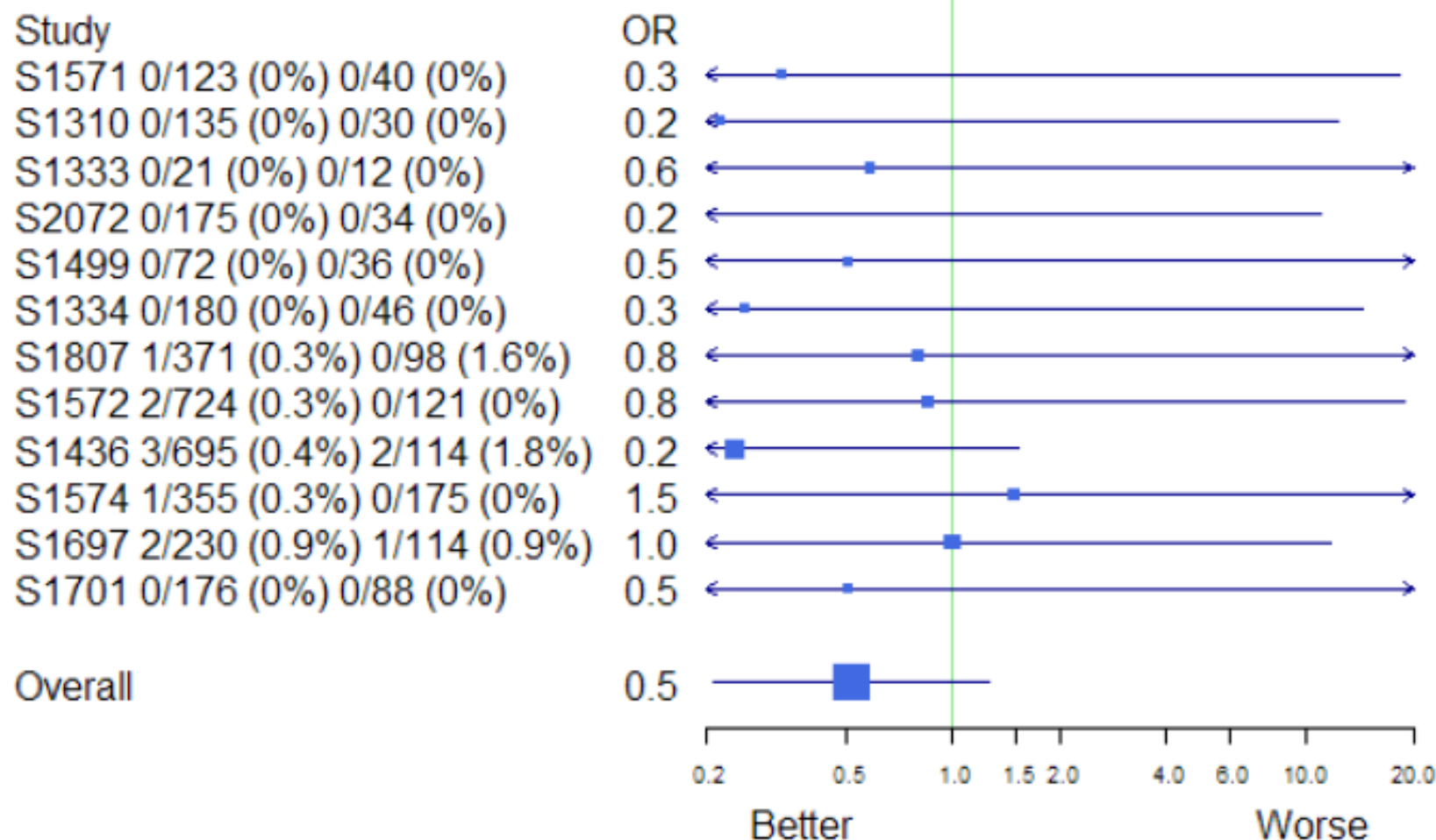
Estimation Methods for Incidence Ratio

- **Cochran Mantel-Haenszel (CMH):**
 - + Well established method for incidence ratio
 - Omits studies with 0 events in both groups
 - With infrequent events assumptions may not be met
- **Exact:**
 - + Assumptions are met even with infrequent events
 - Omits studies with 0 events in both groups
 - 95% CI tends to be conservative
- **Fixed Effects Mantel-Haenszel Meta-Analysis with continuity correction (FEMA):**
 - + Includes all studies
 - Continuity correction can be very influential

Liraglutide vs. Placebo

Custom MACE, Population A, FEMA Method

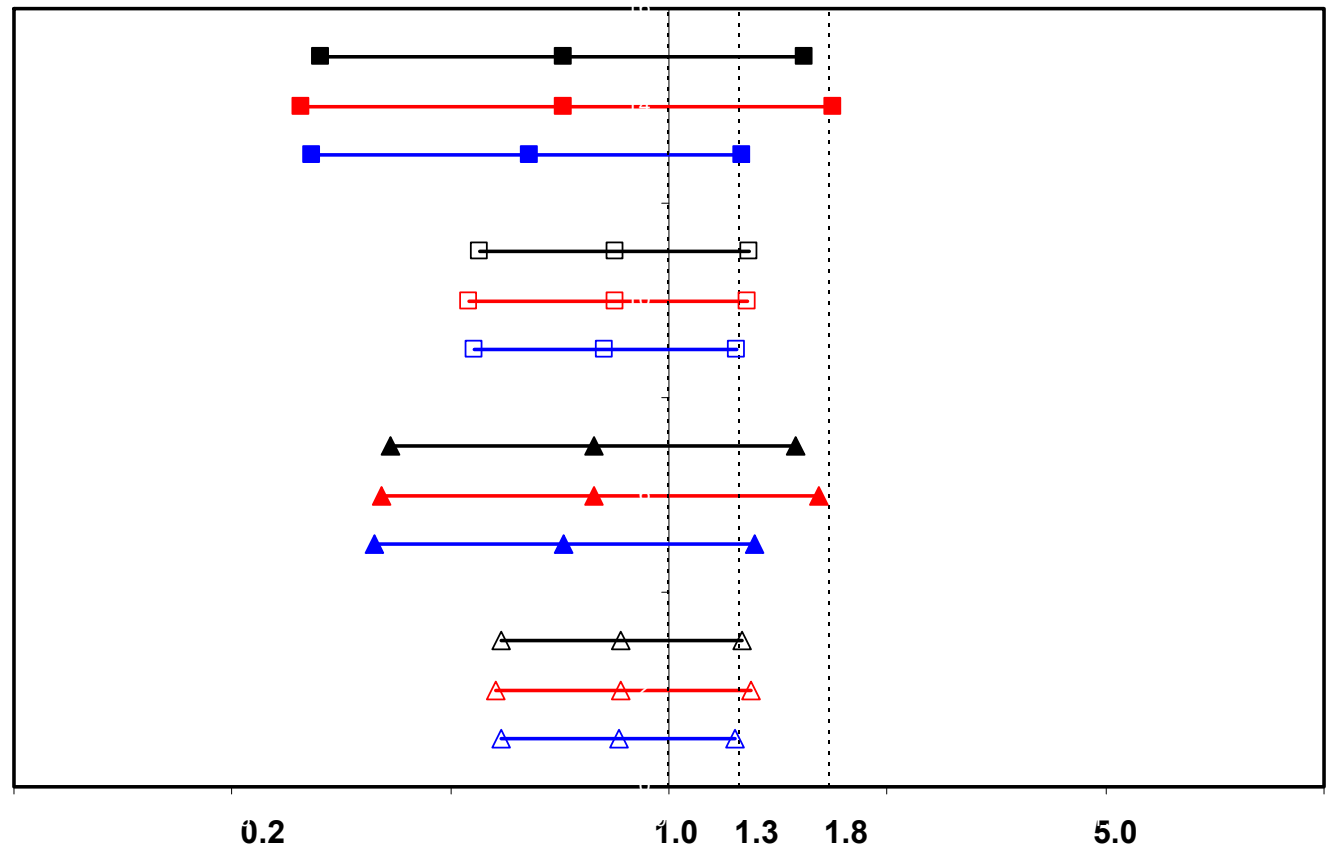
Figure II.C.1: Forest Plot for FDA Custom Endpoint, Liraglutide vs. Placebo, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population A. Values to the left of 1.0 favor liraglutide.



Liraglutide vs. Active (Subgroup of 9 Studies)

Liraglutide vs Active, all TEAE, 95% CI

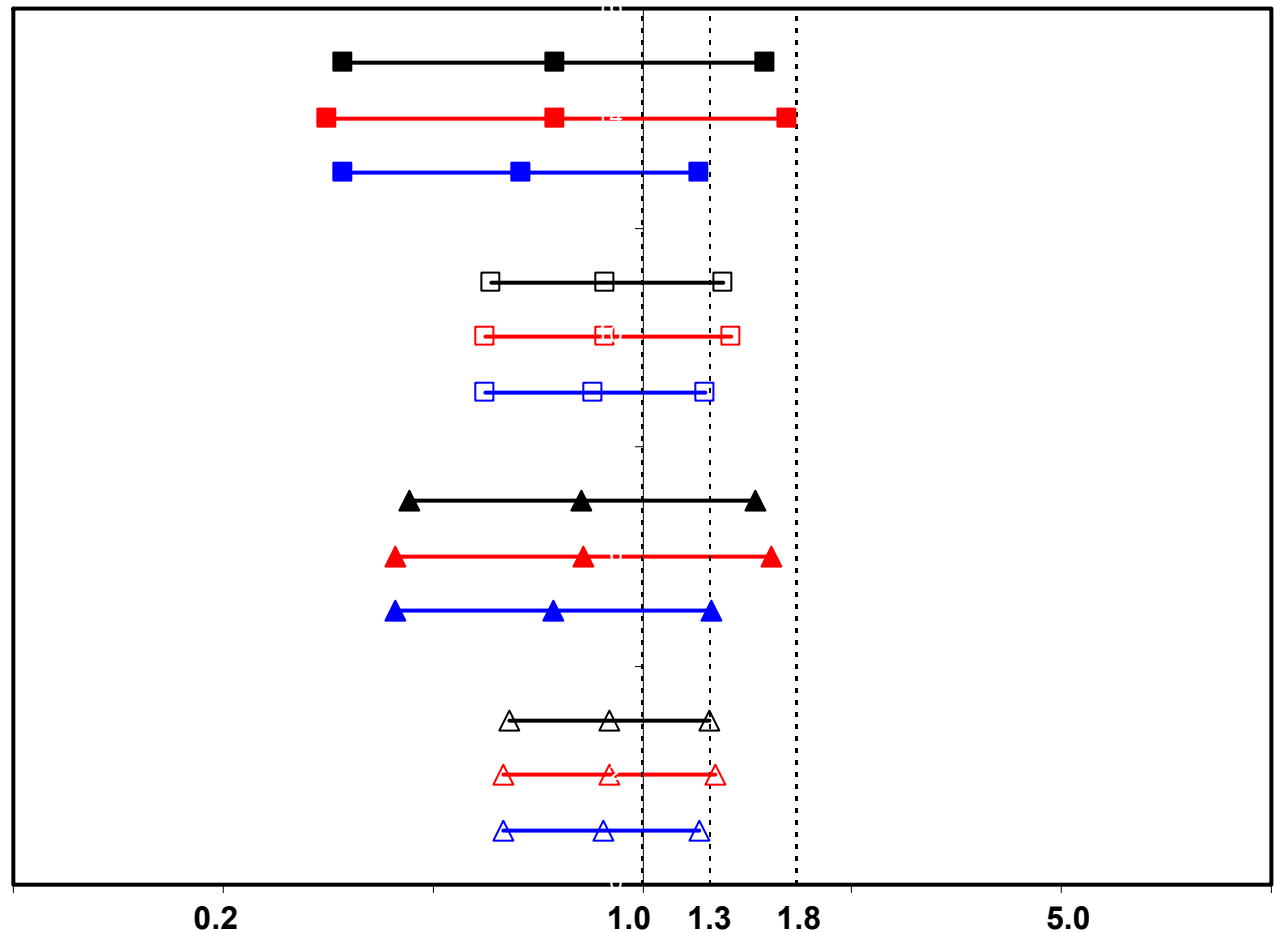
- Custom, CMH, Pop A
- Custom, Exact, Pop A
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- SMQ Broad, CMH, Pop A
- SMQ Broad, Exact, Pop A
- SMQ Broad, FEMA, Pop A
- ▲— Custom, CMH, Pop B
- ▲— Custom, Exact, Pop B
- ▲— Custom, FEMA, Pop B
- △— SMQ Broad, CMH, Pop B
- △— SMQ Broad, Exact, Pop B
- △— SMQ Broad, FEMA, Pop B



Liraglutide vs. Total Comparator (All 15 Studies)

Liraglutide vs Total Comparator, all TEAE, 95% CI

- Custom, CMH, Pop A
- Custom, Exact, Pop A
- Custom, FEMA, Pop A
- SMQ Broad, CMH, Pop A
- SMQ Broad, Exact, Pop A
- SMQ Broad, FEMA, Pop A
- ▲— Custom, CMH, Pop B
- ▲— Custom, Exact, Pop B
- ▲— Custom, FEMA, Pop B
- △— SMQ Broad, CMH, Pop B
- △— SMQ Broad, Exact, Pop B
- △— SMQ Broad, FEMA, Pop B



MACE Results: LGT vs Total Comparator

- **Point estimates <1**
- **Upper bound of 95% CI <1.8**
- **Upper bound of 95% CI usually >1.3**
- **Not very sensitive to analysis method, i.e. similar results for different endpoints, populations, event seriousness groupings and statistical analysis methods**

Incidence Ratio, Liraglutide vs Total Comparator, Novo Stratified Asymptotic CMH Analysis

Endpoint		Event Type		Pop		Point Est	95% CI Upper Bound
FDA Custom	Broad SMQ	All TEAE	Serious Only	A	B		
x		x		x		0.72	1.61
	x	x		x		0.87	1.34
x			x	x		0.69	1.62
	x		x	x		0.67	1.41
x		x			x	0.79	1.54
	x	x			x	0.88	1.28
x			x		x	0.76	1.57
	x		x		x	0.83	1.56

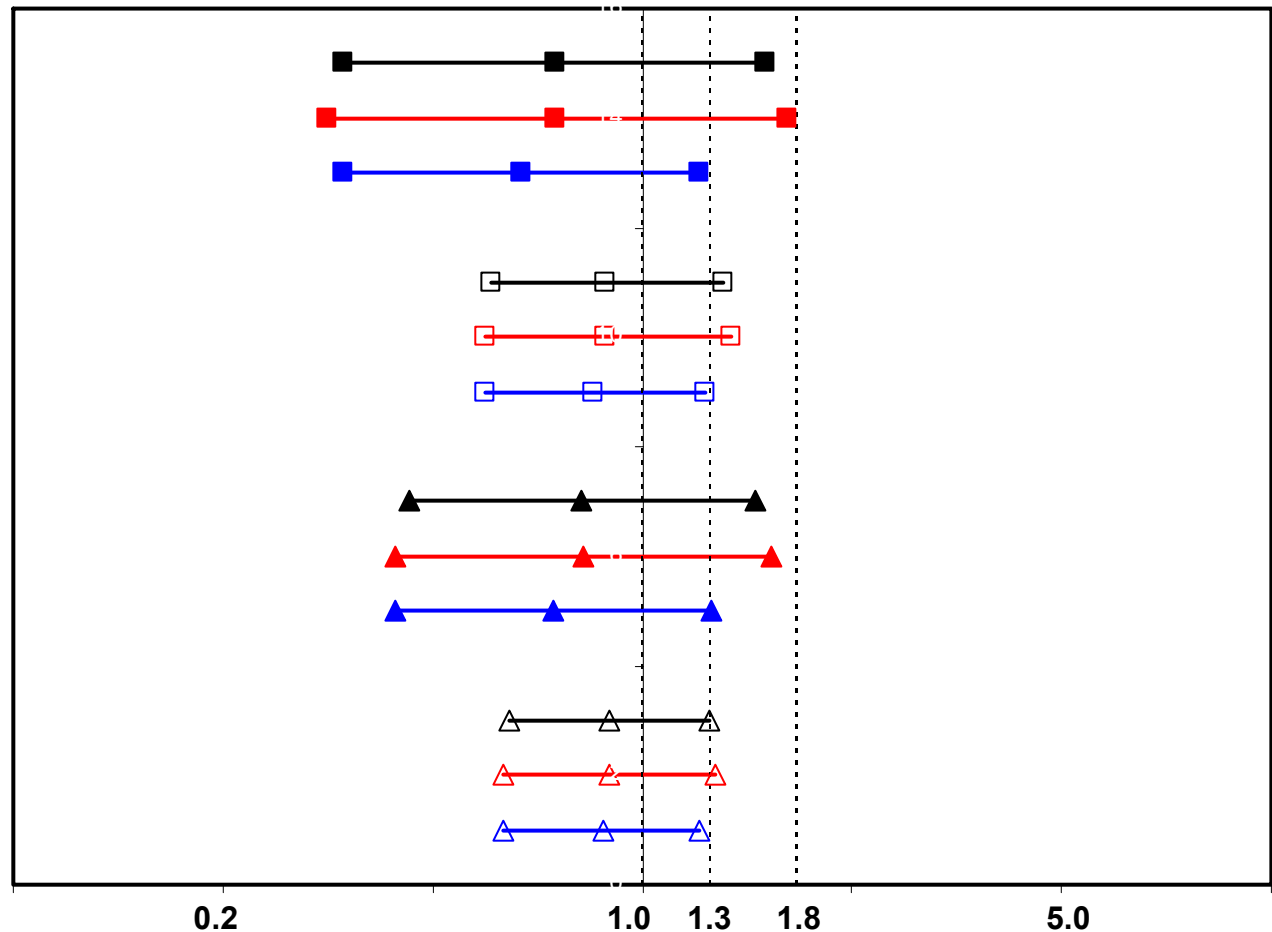
Incidence Ratio, Liraglutide vs Total Comparator, FDA Analyses, All (Serious + Nonserious) Treatment-emergent MACE, Broad SMQ and FDA Custom Endpoints

Analysis Method		Endpoint		Pop		Point Est	95% CI Upper Bound
Exact	FE MH with CC	FDA Custom	Broad SMQ	A	B		
X		X		X		0.72	1.74
X			X	X		0.86	1.41
X		X			X	0.80	1.64
X			X		X	0.90	1.36
	X	X		X		0.63	1.24
	X		X	X		0.83	1.27
	X	X			X	0.71	1.30
	X		X		X	0.86	1.24

Liraglutide vs. Total Comparator

Liraglutide vs Total Comparator, all TEAE, 95% CI

- Custom, CMH, Pop A
- Custom, Exact, Pop A
- Custom, FEMA, Pop A
- SMQ Broad, CMH, Pop A
- SMQ Broad, Exact, Pop A
- SMQ Broad, FEMA, Pop A
- ▲— Custom, CMH, Pop B
- ▲— Custom, Exact, Pop B
- ▲— Custom, FEMA, Pop B
- △— SMQ Broad, CMH, Pop B
- △— SMQ Broad, Exact, Pop B
- △— SMQ Broad, FEMA, Pop B



MACE Results: Subgroup Analysis of LGT vs Active Comparator

- **Point estimates <1**
- **Upper bound of 95% CI usually <1.8**
- **Upper bound of 95% CI usually >1.3**
- **Somewhat sensitive to analysis method, but fairly similar results for different endpoints, populations, event seriousness groupings and statistical analysis methods**

Incidence Ratio, Liraglutide vs Active Comparator, Novo Stratified Asymptotic CMH Analysis

Endpoint		Event Type		Pop		Point Est	95 % CI Upper Bound
FDA Custom	Broad SMQ	All TEAE	Serious Only	A	B		
X		X		X		0.68	1.66
	X	X		X		0.82	1.32
X			X	X		0.63	1.57
	X		X	X		0.61	1.38
X		X			X	0.76	1.61
	X	X			X	0.85	1.29
X			X		X	0.68	1.47
	X		X		X	0.74	1.47

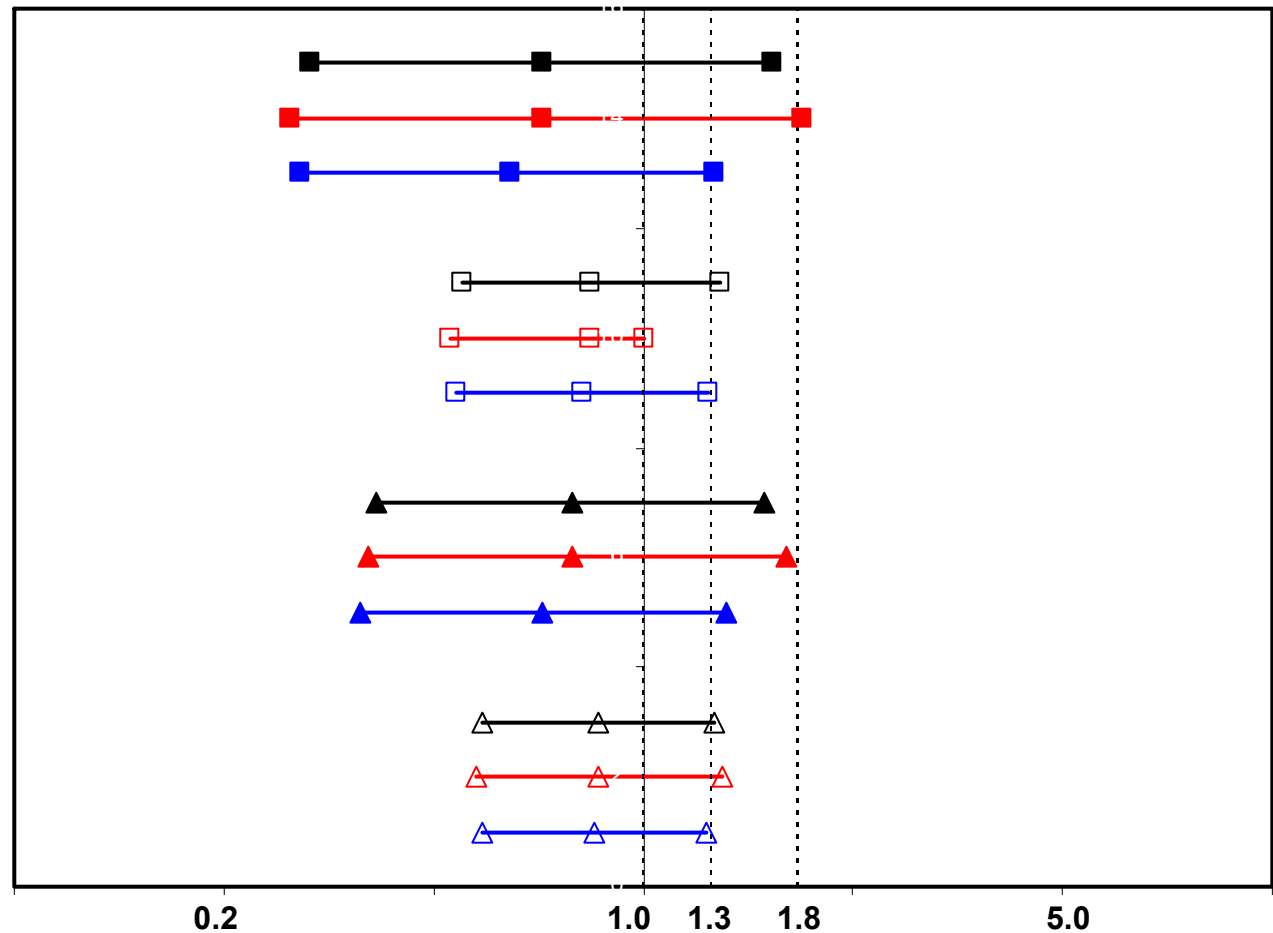
Incidence Ratio, Liraglutide vs Active Comparator, FDA Analyses, All (Serious + Nonserious) Treatment-emergent MACE, Broad SMQ and FDA Custom Endpoints

Analysis Method		Endpoint		Pop		Point Est	95% CI Upper Bound
Exact	FE MH with CC	FDA Custom	Broad SMQ	A	B		
X		X		X		0.68	1.83
X			X	X		0.82	1.33
X		X			X	0.76	1.72
X			X		X	0.84	1.35
	X	X		X		0.60	1.31
	X		X	X		0.79	1.28
	X	X			X	0.68	1.37
	X		X		X	0.83	1.27

Subgroup Analyses: Liraglutide vs Active

Liraglutide vs Active, all TEAE, 95% CI

- Custom, CMH, Pop A
- Custom, Exact, Pop A
- Custom, FEMA, Pop A
- SMQ Broad, CMH, Pop A
- SMQ Broad, Exact, Pop A
- SMQ Broad, FEMA, Pop A
- ▲— Custom, CMH, Pop B
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- ▲— Custom, FEMA, Pop B
- △— SMQ Broad, CMH, Pop B
- △— SMQ Broad, Exact, Pop B
- △— SMQ Broad, FEMA, Pop B



MACE Results: Subgroup Analysis of LGT vs Placebo

- **Point estimates often >1**
- **Upper bound of 95% CI often >1.8**
- **Upper bound of 95% CI usually >1.3**
- **Sensitive to analysis method: varying results for different endpoints, populations, event seriousness groupings and statistical analysis methods**
- **Guidance does not require applicants to meet specified 95% CI boundary limits for subgroup analyses**

Incidence Ratio, Liraglutide vs Placebo, Novo Stratified Asymptotic CMH Analysis

Endpoint		Event Type		Pop		Point Est	95% CI Upper Bound
FDA Custom	Broad SMQ	All TEAE	Serious Only	A	B		
X		X		X		0.80	2.83
	X	X		X		1.04	2.16
X			X	X		0.94	4.58
	X		X	X		0.90	3.22
X		X			X	0.92	2.83
	X	X			X	1.02	1.92
X			X		X	1.32	6.20
	X		X		X	1.33	4.60

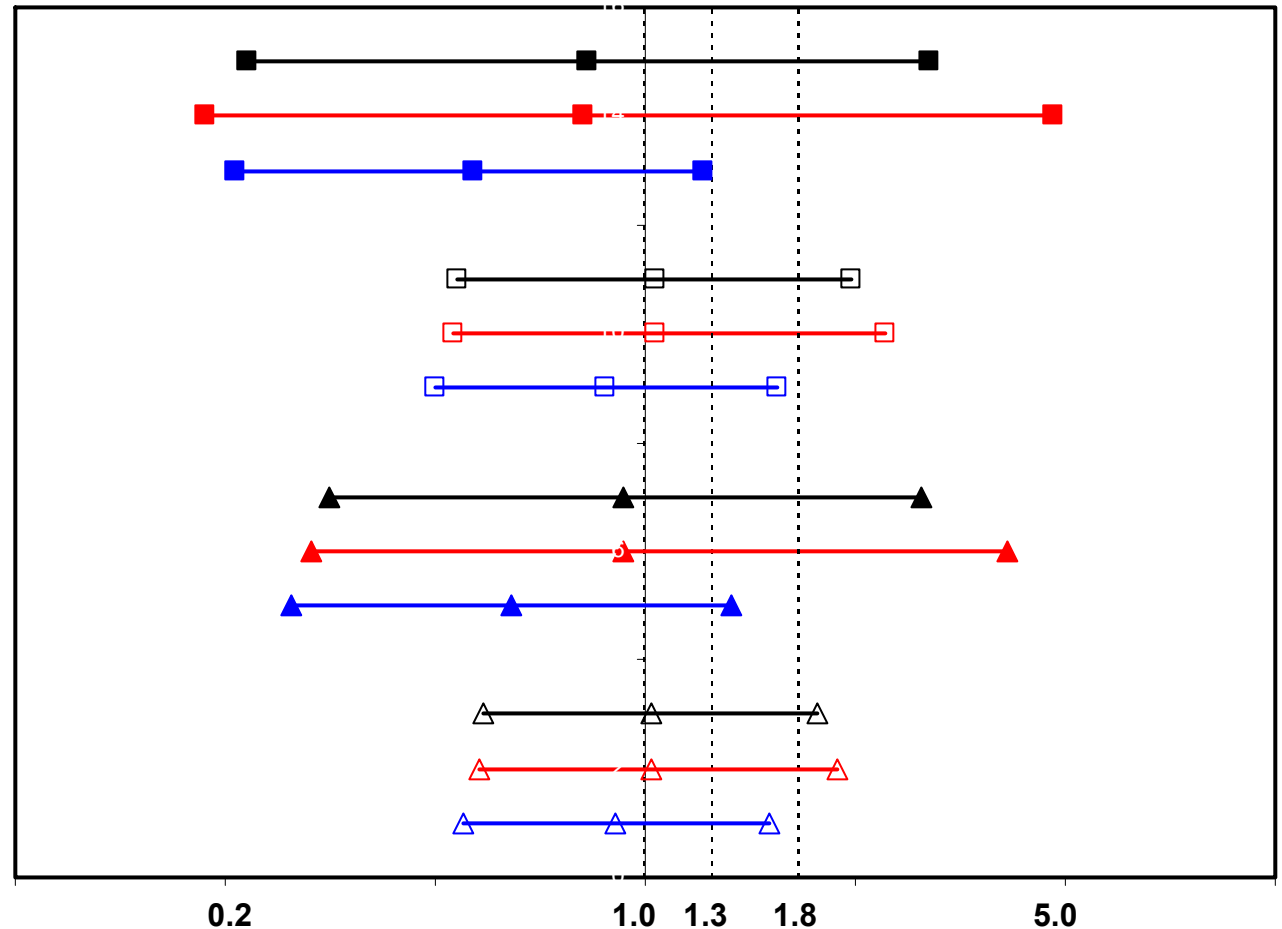
Incidence Ratio, Liraglutide vs Placebo, FDA Analyses, All (Serious + Nonserious) Treatment-emergent MACE, Broad SMQ and FDA Custom Endpoints

Analysis Method		Endpoint		Pop		Point Est	95% CI Upper Bound
Exact	FE MH with CC	FDA Custom	Broad SMQ	A	B		
X		X		X		0.78	4.76
X			X	X		1.04	2.17
X		X			X	0.92	3.97
X			X		X	1.10	2.31
	X	X		X		0.52	1.25
	X		X	X		0.86	1.65
	X	X			X	0.60	1.39
	X		X		X	0.89	1.60

Subgroup Analyses: Liraglutide vs Placebo

Liraglutide vs Placebo, all TEAE, 95% CI

- Custom, CMH, Pop A
- Custom, Exact, Pop A
- Custom, FEMA, Pop A
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- △ SMQ Broad, CMH, Pop B
- △ SMQ Broad, Exact, Pop B
- △ SMQ Broad, FEMA, Pop B



Why Were Some Point Estimates >1 for Subgroup Analyses of LGT vs PBO?

- **Probably not due to lower baseline risk among placebo-treated patients**
- **Analyses stratified by trial**
- **Trials that used a placebo control were add-on trials, and not monotherapy trials in naïve patients**
- **Trials that used add-on placebo did not have gross imbalances in baseline cardiovascular risk factors or concomitant medication use**
- **More rescue of add-on pbo-treated patients may have meant that fewer of these patients were available to have events. Analyses that took patient-year exposure into account had somewhat lower point estimates for LGT vs PBO.**

Why Were Results for Subgroup Analyses of LGT vs PBO Sensitive to Analysis Method?

- **Low event rates contributed to sensitivity to method**
- **Largest number of placebo group patients with event for any analysis = 13 patients (Broad SMQ, All TEAE, Pop B)**
- **For FDA Custom, Serious AE, Pop A, number of placebo group patients with event = 2**
- **Low event rates also contributed to some sensitivity to method seen for the analyses of LGT to active comparator**
- **Low event rates present a challenge to assessing the risk of truly clinically significant CV events for liraglutide**

Examples of Raw Numbers of Patients with Events, and Effect of Changes in Analysis Scenario

Endpoint	Analysis Scenario	Change to Scenario	LGT N=4257 n (%)	Total Comp N=2381 n (%)	PBO N=907 n (%)	Reason for Decrease?
Broad SMQ	Broad, All MACE, Pop B*	n/a	69 (1.62)	45 (1.89)	13 (1.43)	n/a
	Broad, All MACE, Pop A	Pop B to Pop A	51 (1.20)	35 (1.47)	9 (0.99)	omission of extension data
	Broad, Serious MACE, Pop A	All MACE to Serious MACE	16 (0.38)	16 (0.67)	3 (0.33)	omission of nonserious CPK events
FDA Custom	Custom, All MACE, Pop B	n/a	21 (0.49)	17 (0.71)	4 (0.44)	CPK events not in Custom
	Custom, All MACE, Pop A	Pop B to Pop A	13 (0.31)	13 (0.55)	3 (0.33)	omission of extension data
	Custom, Serious MACE, Pop A**	All MACE to Serious MACE	11 (0.26)	12 (0.50)	2 (0.22)	omission of nonserious non-CPK events

* Scenario with largest numbers of patients with events

** Scenario with smallest numbers of patients with events

Most Commonly Occurring Event Terms

Event	Total N = 6638 n (%)	LGT N = 4257 n (%)	Comp N = 2381 n (%)	In Broad SMQ?	In FDA Custom?
Blood CPK incr	52 (0.8)	32 (0.8)	20 (0.8)	Y	
MI	15 (0.2)	8 (0.2)	7 (0.3)	Y	Y
Acute MI	12 (0.2)	7 (0.2)	5 (0.2)	Y	Y
Carotid artery stenosis	7 (0.1)	2 (<0.1)	5 (0.2)	Y	
TIA	6 (0.1)	4 (0.1)	2 (0.1)	Y	
Cerebral infarction	4 (0.1)	2 (<0.1)	2 (0.1)	Y	Y
CVA	4 (0.1)	3 (0.1)	1 (<0.1)	Y	Y

Total Mortality

- 4 post-randomization deaths for LGT-treated patients
- 3 post-randomization deaths for comparator-treated patients
- 2 of the comparator-treated patients who died had MI listed as cause of death
- Overall death rate low and no pattern of causation

Summary of MACE Observations

- Development program not prospectively designed to permit systematic evaluation of CV events
- CV events did not undergo preplanned adjudication, and adequate data were not available for post hoc adjudication
- Development program did not include a large number of high risk patients
- Few major CV events occurred; this presents a challenge to assessment of CV risk

Summary of MACE Observations (cont)

- For LGT vs total comparator, point estimates <1 ; upper bounds of 95% CI <1.8 , but usually >1.3 . Not very sensitive to analysis method.
- For LGT vs active comparator (subgroup analyses), point estimates <1 ; most upper bounds of 95% CI <1.8 and >1.3 . Somewhat sensitive to analysis method.
- For LGT vs PBO (subgroup analyses), point estimates often >1 ; most upper bounds of 95% CI >1.8 . Sensitive to analysis method.

Summary of MACE Observations (cont)

- **Low event rates contributed to sensitivity to method for subgroup comparisons to PBO and, to a lesser extent, for subgroup comparisons to active comparator**
- **Guidance does not require applicants to meet specified 95% CI boundary limits for subgroup analyses**
- **No apparent relationship between liraglutide dose and risk of MACE**
- **Low rate of total mortality; no cause-specific pattern**

Thyroid Cancer and Calcitonin



Endocrinologic and Metabolic Drugs Advisory Committee
2 April 2009

Summary of Observations from Animal Studies

- **LGT associated with C-cell tumors in mice and rats, in both genders, at clinically relevant exposures**
- **A similar signal is being noted in interim carcinogenicity data for some other long-acting (q day and longer) GLP-1 analogues in development**
- **Mechanistic studies may not have definitively demonstrated that this risk is specific to rodents**
- **No drug that has caused C-cell tumors in 2 species is known to have been approved**
- **Very rare for a drug that has caused tumors (of any cell type) in 2 species, in both genders, at clinically relevant exposures, to have been approved, regardless of mechanism**

Medullary Thyroid Carcinoma Background

- **Relatively rare**
- **Arises from C-cells of thyroid gland**
- **Sporadic and familial forms**
- **Often have RET mutations; useful in screening kindreds**
- **Excess calcitonin secretion often occurs**

Medullary Thyroid Carcinoma (cont)

- **Relatively indolent, although not always**
- **Clinical trial program might be too short to detect indolent tumors**
- **Early complete surgical excision probably only curative option. If nonresectable, patients usually die of MTC.**
- **To date, no clearly-described association between a particular drug and known increased risk of MTC**

Medullary Thyroid Carcinoma Cases

- **One case of MTC recently reported in a comparator-treated patient**
- **Two cases of “medullary carcinoma in situ” (neoplastic C-cell hyperplasia) reported (one LGT-treated and one comparator-treated)**

Patient 770001

(MTC, Comparator-treated)

- 61 yo man
- Baseline calcitonin 1023 ng/L (uln 8.4)
- Treated with glimepiride, metformin and insulin glargine for 144 days. Not treated with LGT.
- Ultrasound showed right lobe “completely filled by” nodule (3.9 cm max diam) with other nodules/cysts in left lobe
- FNA inconclusive
- After study completion, total thyroidectomy
- Pathology consistent with medullary thyroid carcinoma (typical structural features and multiple stains positive), with extracapsular spread, and endovascular and endolymphatic propagation

Patient 175008 (“medullary carcinoma in situ”, LGT-treated)

- 64 yo man
- Baseline calcitonin 22.3 ng/L (uln 8.4)
- Received LGT 1.8 mg for 26 days
- Thyroid ultrasound: “small hypoechoic lesion” left upper pole
- Pathology report, and subsequent confirmatory consultation, consistent with bilateral neoplastic C-cell hyperplasia, “also known as ‘medullary carcinoma in situ’ ”
- Numerous perifollicular aggregations of atypical C-cells
- 1 mm focus of papillary thyroid carcinoma also noted

Patient 224012 (“medullary carcinoma in situ”, comparator-treated)

- 64 yo man
- Normal calcitonin at baseline
- Baseline “struma nodosa”
- Received metformin for 390 days and glimepiride for 370 days
- Three months after study entry, calcitonin 3.54 pmol/L (uln 2.46)
- Abnormal pentagastrin stim test near end of study
- Eight months after study, total thyroidectomy
- MNG and bilateral neoplastic C-cell hyperplasia diagnosed. Immunohistochemical staining for calcitonin positive in aggregates of cells around pre-existing follicles.

Papillary Thyroid Cancer Cases

ID	Age/Sex	Tx	Exp
016004	70 y f	LGT 0.6	99 d
261006	62 y f	LGT 1.2	356 d
175008	64 y m	LGT 1.8	26 d
506001	59 y m	LGT 1.8 + GLIM	175 d
326016	53 y f	LGT 1.8 + MET + RSG	50 d
221008	54 y m	LGT 1.8 + MET	364 d
326008	59 y m	MET + RSG	61 d

Papillary Thyroid Cancer Cases (cont)

ID	Calcitonin Incr PreOp?	Tumor Size	CCH?
016004	N	T1 (<2 cm)	N
261006	Y	1 mm	Y
175008	Y	1 mm	Y
506001	Y	?	N
326016	Y	9 mm, 2.5 mm, 1 mm	N
221008	Y	2 mm	Y
326008 (non-LGT)	Y	1 mm	N

C-Cell Hyperplasia Cases

- **3 LGT cases (excluding case of “MTC in situ”)**
- **No other comparator cases (excluding case of MTC and case of “MTC in situ”)**
- **All diagnosed through clinical trial monitoring of calcitonin**
- **Pre-operative calcitonin elevations mild**

C-Cell Hyperplasia Case Features

ID and Gender	Tx	Exp (total)	BL C-tonin (ng/L) ULN: M = 8.4 F = 5.0	PreOp Static C- tonin	PreOp Stim C- tonin Peak ULN: M = 130 F = 90	Path
228002 M	LGT 0.6	190 d	21.5	15	119	Diffuse CCH
261006 F	LGT 1.2	484 d	?	?	94	Diffuse CCH
221008 M	LGT 1.8	363 d	15.1	22.3	203	Diffuse CCH
175008 M	LGT 1.8	28 d	22.3	?	?	"MTC in situ"
224012 M	MET + GLIM	370 d	"normal"	12.1	"abnl"	"MTC in situ"

Calcitonin

- Synthesized in several mammalian tissues, but thyroid C-cells primary site
- Normal human circulating levels very low
- Inhibitory effect on osteoclast-mediated bone resorption
- Multiple stimuli for release
- Clinical marker for medullary thyroid carcinoma, but there are controversies regarding calcitonin use for screening (PPV probably low for mild elevations)
- No experience with using calcitonin to screen for potential drug-induced MTC

Calcitonin Testing for Liraglutide

- **Static testing in 5 longterm trials and some shorter trials**
- **Calcium stimulation testing on subpopulation from 2 longterm trials**
- **Did not demonstrate a liraglutide-associated risk of marked elevation in calcitonin**
- **However, liraglutide may have some effect on calcitonin levels**

Calcitonin Category Shifts for LGT-Treated Women, BL-Wks 26/28, Longterm Trials

Percentage who shifted from <LLOQ to within range of quantitation:

- **Active comparator 14.5%**
- **Placebo 14.8%**
- **LGT 0.6 mg 15.6%**
- **LGT 1.2 mg 16.8%**
- **LGT 1.8 mg 19.2%**

Percentage of Patients with Any Upward Calcitonin Category Shift, BL-26/28 Wks, Longterm Trials

Tx	Both Genders	Women	Men
PBO	16.0	15.2	16.6
AC	17.2	16.1	18.2
LGT 0.6	17.3	17.1	17.8
LGT 1.2	16.2	17.2	15.1
LGT 1.8	20.0	20.0	20.1

Calcitonin Values, Long-Term Trials (mean in ng/L, with 95% CI)

Tx	Wk 12	Wk 26
PBO	0.67 (0.63, 0.73)	0.89 (0.83, 0.95)
AC	0.70 (0.66, 0.74)	0.97 (0.91, 1.02)
LGT 0.6	0.78 (0.72, 0.84)	0.96 (0.90, 1.04)
LGT 1.2	0.78 (0.73, 0.83)	0.99 (0.94, 1.05)
LGT 1.8	0.76 (0.72, 0.81)	1.01 (0.95, 1.06)

Relative Difference in Mean Calcitonin Values, Wk 12, Longterm Trials

Comparison	Rel Diff, % (95% CI)	p-value
LGT 1.8 vs PBO	13.0 (4.8, 21.8)	0.0014
LGT 1.2 vs PBO	15.4 (6.7, 24.7)	0.0003
LGT 0.6 vs PBO	15.2 (5.5, 25.7)	0.0015
LGT 1.8 vs AC	8.6 (2.2, 15.4)	0.0080
LGT 1.2 vs AC	10.9 (3.9, 18.3)	0.0017
LGT 0.6 vs AC	10.7 (2.6, 19.4)	0.0084
AC vs PBO	4.0 (-3.7, 12.4)	0.3118

Relative Difference in Mean Calcitonin Values, Wk 26, Longterm Trials

Comparison	Rel Diff, % (95% CI)	p-value
LGT 1.8 vs PBO	13.6 (6.1, 21.6)	0.0003
LGT 1.2 vs PBO	11.8 (4.1, 20.2)	0.0023
LGT 0.6 vs PBO	8.8 (0.3, 17.9)	0.0428
LGT 1.8 vs AC	4.3 (-1.6, 10.4)	0.1542
LGT 1.2 vs AC	2.7 (-3.5, 9.2)	0.4024
LGT 0.6 vs AC	-0.1 (-7.1, 7.3)	0.9683
AC vs PBO	8.9 (1.5, 16.9)	0.0181

Calcitonin Relative (%) Differences Between Treatment Grps at 26 Wks, Longterm Trials

All trials

Lira 1.80 vs. Placebo

Lira 1.20 vs. Placebo

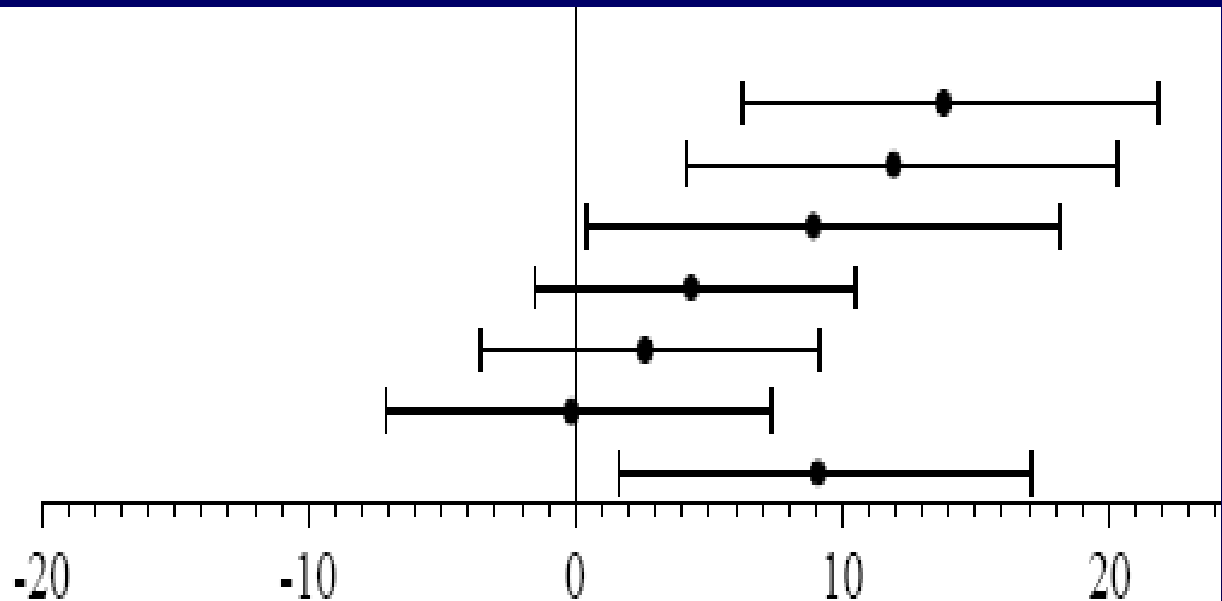
Lira 0.60 vs. Placebo

Lira 1.80 vs. Active

Lira 1.20 vs. Active

Lira 0.60 vs. Active

Active vs. Placebo



Summary of Thyroid Cancer and Calcitonin Observations

- **LGT associated with C-cell tumors in mice and rats, in both genders, at clinically relevant exposures**
- **A similar animal signal is being noted in interim carcinogenicity data for some other long-acting (q day and longer) GLP-1 analogues in development**
- **Mechanistic studies may not have definitively demonstrated that this risk is specific to rodents**
- **No drug that has caused C-cell tumors in 2 species is known to have been approved**
- **Very rare for a drug that has caused tumors (of any cell type) in 2 species, in both genders, at clinically relevant exposures, to have been approved, regardless of mechanism**

Summary of Thyroid Cancer and Calcitonin Observations (cont)

- No clear MTC for any LGT-treated patients, but might not expect to see this relatively indolent tumor over the duration of the development program
- 1 case of neoplastic C-cell hyperplasia (“MTC in situ”) for LGT and 1 case for comparator
- Papillary thyroid cancer 6 cases for LGT and 1 for comparator (ratio approx 3:1)
- Papillary thyroid cancer cases mostly microcarcinomata, with surgery prompted by per-protocol calcitonin screening
- 3/6 LGT pts who had papillary thyroid Ca also had CCH (2 diffuse, 1 neoplastic)
- 1 additional case of diffuse CCH for LGT

Summary of Thyroid Cancer and Calcitonin Observations (cont)

- Use of calcitonin to screen for MTC controversial
- No experience using calcitonin to screen for drug-induced MTC
- Did not demonstrate a liraglutide-associated risk of marked elevation in calcitonin in humans
- In longterm trials, dose-dependent trend for LGT-treated women to shift from below LLOQ to within range of quantitation. LGT > PBO or AC.
- Upward shifts of calcitonin more common with 1.8 mg (highest) dose in men and women than with lower LGT doses and comparator, but no LGT dose-dependence

Summary of Thyroid Cancer and Calcitonin Observations (cont)

- **Mean changes in calcitonin were small**
- **Uncertain clinical significance of small changes in calcitonin in this setting**
- **Analyses of differences in mean calcitonin levels were exploratory; interpret statistical significance with caution**
- **At Week 12, mean calcitonin levels stat sig higher for all doses of LGT than for PBO or AC**
- **At Week 26, mean calcitonin levels stat sig higher for LGT vs PBO, but not for LGT vs AC. Dose dependent trend for both LGT vs PBO and LGT vs AC**

Summary of Thyroid Cancer and Calcitonin Observations (cont)

- **Thyroid nodules are common in the general population; most are benign**
- **A thyroid nodule associated with an increased calcitonin level might be more likely to go to surgery**
- **Enhanced monitoring with calcitonin or ultrasound might result in increased rate of thyroidectomy**
- **Thyroidectomy has surgical and anesthetic risks**

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